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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/799,782	03/15/2004	Axel Ullrich	034536-1243	9104

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EXAMINER	
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ART UNIT	PAPER NUMBER
1647	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/799,782	ULLRICH ET AL.	
	Examiner	Art Unit	
	/Lorraine Spector/ Ph.D.	1647	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *09 April 2008 and 29 August 2008*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *5 and 6* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *5 and 6* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

In the previous Office Action, the Examiner noted that applicants having stated on the record that the sequences in figures 11-1 to 11-4 are *different* than the sequence submission, the Examiner finds that the application is not in full compliance with sequence rules. Applicants are required to amend the specification to be in full compliance with sequence rules in response to this office action, and, if needed to submit a new CRF reflecting the different sequences, along with a new paper copy of the sequence listing and statement that the CRF and paper copy are identical, in addition to amending the specification to reflect the newly added sequence identifiers.

In the response filed 4/9/2008, applicants corrected the figure numbers, and inserted SEQ ID NO: 2 into the brief description thereof. However, applicants have not reconciled their previous statement that the sequences in the figures are *different* than those in the CRF.

Appropriate correction or explanation is required.

The Examiner finds basis for the new limitation that the claimed species is truncated at residue 806 in the specification as originally filed.

The new Abstract of the Disclosure is acknowledged.

Claim Interpretation

It is noted that the recitation in claims 5 and 6 of "cell line" is taken to indicate an *in vitro* cell population, and not to read on an animal or human.

Double Patenting

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. A nonstatutory obviousness-type double patenting rejection

is appropriate where the conflicting claims are not identical, but at least one examined application claim is not patentably distinct from the reference claim(s) because the examined application claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent either is shown to be commonly owned with this application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement.

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

Claims 5-6 remain rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1-9 of U.S. Patent No. 5,851,999. Although the conflicting claims are not identical, they are not patentably distinct from each other because claims 1-4 would be anticipated by the patented claims, as the claims are related as sub-genus to genus. With respect to claims 5 and 6, the person of ordinary skill in the art would immediately grasp, upon reading the patented claims, the desirability of making a cell line as currently claimed to produce the viral particles used in the patented pharmaceutical compositions. Accordingly, the claims are obvious over the patented claims.

Applicants previously indicated an intent to submit a terminal disclaimer. However, in the response filed 4/9/2008, applicants requested that this rejection be held in abeyance. Applicants are advised that such abeyance is only for the purpose of filing a terminal disclaimer. No traversal of the rejection will be considered timely at such time as the claims may have been found otherwise allowable.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 5-6 remain rejected under 35 U.S.C. § 103 as being unpatentable over Lemischka, U.S. Patent Number 5,185,438, Matthews et al. (PNAS 88:9026) and Terman et al. (BBRC 187:1579), in view of Ullrich et al. (Cell 61:203), and Ueno et al., (Science 252:844, Ueno-1 and JBC 267:1470, Ueno-2), all references cited by applicants.

In the response filed 8/9/2008, applicants indicate that in the *KSR* decision, the court noted that it is important to find a reason to combine the cited prior art, and that such analysis should be specific.

This argument has been fully considered but is not deemed persuasive because going back to the first action on the merits at page 7, the Examiner stated:

It would have been obvious to the person of ordinary skill in the art at the time the invention was made to modify the nucleic acids and recombinant vectors of Matthews et al., Terman et al. or Lemischka to delete all or a portion of the sequence encoding the intracellular domain as taught by Ullrich and Ueno. The person of ordinary skill in the art would have been motivated to make such modifications in view of the teachings of Terman et al., specifically that Flk-1 is the murine homologue of the KDR receptor disclosed by Terman et al., and that it would be desirable to investigate the dimeric combinations in which the receptor occurs, and the relationship of such to the physiological responses known to occur in response to the ligand, VEGF (see teachings of Terman et al. as discussed above), and would further have been motivated by the teachings of Ullrich and Ueno that such deletions result in signaling incompetent receptors that act in a dominant-negative fashion *in vivo,* and that such results are expected to be generally applicable to tyrosine kinase receptors. The teachings of the secondary references would have provided further incentive to make such derivatives for the purpose of inhibiting the biological function of the receptor *in vivo,* which function was taught by Terman as being involved in angiogenesis. It would further have been obvious to incorporate such truncated coding sequences in a retroviral vector (and cell line containing such and producing infectious particles) because retroviral vectors are known in the art to be useful for the efficient vectors for the introduction of DNA into eukaryotic cells. With respect to the specific limitations in the claims as to termination of the coding sequence at the portion encoding amino acid 806, as this particular location falls within the cytoplasmic domain but results in the exclusion of the tyrosine kinase portion of the molecule, it is deemed to be *prima facie* obvious especially in view of the teachings of Ullrich and Ueno that teach toward deleting the tyrosine kinase domain of the receptors.

Therefore, specific motivation is found, in that one would expect the truncated receptor to be dominant negative, and useful for inhibiting angiogenesis, which, the Examiner notes, is of great utility in medicine, especially treatment of cancer.

The Court explained that "[t]he combination of familiar elements. is likely to be obvious when it does no more than yield predictable results." *KSR* 127 at 1731. Here, there is no evidence that the results achieved by combining the cited references would predict that a truncated flk-1 consisting of amino acids 1 to 806 would have dominant negative activity. And where no reference suggests any advantage to the combination, the record only supports a finding that the results achieved by the present invention are unexpected and, therefore, not obvious.

Applicants are mixing up two issues. The first is whether it would have been expected that flk-1 consisting of amino acids 1-806 would have dominant negative activity. The Examiner refers back to the first office action on the merits at pages 6-7, wherein it is discussed that Ullrich teaches that kinase deficient growth factor receptors are expected to be signaling incompetent, and the Ueno teachings that truncated FGFR1 and PDGF-beta receptors lacking portions of their cytoplasmic domains had dominant negative signaling activity, i.e., when combined with a "normal" subunit to form a dimer, were incapable of signaling. With respect to finding an "advantage", the art clearly teaches that flk-1 is the human homolog of KDR and is therefore expected to function in angiogenesis, and that making a truncated flk-1 would be expected to inhibit angiogenesis (as taught by Terman), as such would be signaling incompetent. Clearly that would be advantageous.

Also at page 6 of the April response, applicants argue that none of the references suggest that the truncated proteins are related to the Flk-1 receptor protein or that truncated Flk-1 would behave in a similar manner. This argument has been fully considered but is not deemed persuasive for reasons cited at pages 5-6 of the previous Office Action.

At page 7 of the April response, applicants argue that Ueno 1 did not appreciate the mechanism by which related receptors function. This argument has been fully considered but is not deemed persuasive because as stated in the previous rejection, the remaining cited references (including two articles by Ueno), are all drawn to examples in which tyrosine kinase receptors structurally related to the Flk-1 receptor were altered within the cytoplasmic domain, resulting in proteins that formed signaling incompetent dimers, with dominant-negative characteristics. Based upon the structural similarity of Flk-1 to the c-Kit family of receptors, and further in view of Ullrich et al. (Cell 61:203) who teach that although normal in its binding characteristics, the kinase-negative mutant of the EGF receptor was unable to stimulate calcium influx, inositol phosphate formation, Na+/H+ exchange, ..." , continuing "This suggests that all receptor tyrosine kinase signaling activities depend on a functional tyrosine kinase...". The person of ordinary skill in the art would expect a similar mutation in Flk-1 to retain at least normal binding activity, and to be signaling incompetent. One does not have to thoroughly understand the entire biological system to have an expectation that deletion of the intracellular domain would result in signaling incompetent dimers.

Moving on to the response filed 8/29/2008, applicants argue the reference separately at pages 4-6, and not in the combination in which they are cited, An argument that has been found not to be persuasive for reasons of record. Bridging pages 6-7, applicants argue that the possibility of deleting up to 584 residues is not a "finite number", as was found in *KSR*. First, 584 is quite a finite number. Second, it would be obvious to the person of ordinary skill in the art that the fewer residues left of the intracellular domain, the more likely that signaling would be disrupted. Residue 806 is but 26 residues to the intracellular side of the transmembrane domain, giving an almost complete certainty that signaling would be disrupted. Further, Matthews identifies a number of sequences indicative of tyrosine kinases, all further away from the

transmembrane domain than is residue 806 (see figure 1 of Matthews et al. Accordingly, truncation at position 806 is one of a finite number of species, and would be expected to destroy signaling function.

The Examiner's position is supported by the recent finding by the Supreme Court in *KSR v. Teleflex, Inc.* (82 USPQ 2d 1385, 4/30/2007), which held that "a person of ordinary skill has good reason to pursue the known options within his or her technical grasp. If this leads to the anticipated success, it is likely the product not of innovation but of ordinary skill and common sense. In that instance the fact that a combination was obvious to try might show that it was obvious under §103." (See 82 USPQ2d at 1397.) In this case, the prior art gives the person of ordinary skill in the art the motivation and means to make signaling competent forms of flk-1, including at the specified residue, 806, which given its location would be absolutely expected to confer (in this case remove) the function in question, and also gives ample motivation for doing so (inhibition of angiogenesis, for example).

At page 7, applicants argue that one must rely on evidence available at the time the invention was made. As all cited references are properly prior art, this requirement has been met. Finally, applicants argue that the KSR's focus on "identified, predictable solutions" may be a difficult hurdle. This argument has been fully considered but is not deemed persuasive because in this case there is clearly an identified, predictable solution. Applicants invention follows the teachings of the prior art, and achieves exactly the result that would be predicted on the basis of the prior art. There are no unexpected results.

In summary, it remains that the Examiner's position is supported by the recent finding by the Supreme Court in *KSR v. Teleflex, Inc.* (82 USPQ 2d 1385, 4/30/2007), which held that "a person of ordinary skill has good reason to pursue the known options within his or her technical grasp. If this leads to the anticipated success, it is likely the product not of innovation but of ordinary skill and common sense. In that instance the fact that a combination was obvious to try might show that it was obvious under §103." (See 82 USPQ2d at 1397.) In this case, the art provides motivation to pursue the known option of making a deletion of Flk-1 for the purpose of making a signaling incompetent receptor in view of the Terman disclosure , there were a finite number of possible solutions, the person of ordinary skill in the art would have recognized that the closer to the transmembrane domain the deletion were made the more likely the signaling

function would be destroyed, and therefore, there would have had a more than reasonable expectation of success.

Conclusion

Any inquiry concerning this communication or earlier communications from the Examiner should be directed to Lorraine M. Spector. Dr. Spector can normally be reached Monday through Friday, 9:00 A.M. to 3:00 P.M. at telephone number 571-272-0893.

If attempts to reach the Examiner by telephone are unsuccessful, please contact the Examiner's supervisor, Dr. Manjunath Rao, at telephone number 571-272-0939.

Certain papers related to this application may be submitted to Technology Center 1600 by facsimile transmission The faxing of such papers must conform with the notices published in the Official Gazette, 1156 OG 61 (November 16, 1993) and 1157 OG 94 (December 28, 1993) (see 37 C.F.R. § 1.6(d)). NOTE: If Applicant does submit a paper by fax, the original signed copy should be retained by applicant or applicant's representative. NO DUPLICATE COPIES SHOULD BE SUBMITTED so as to avoid the processing of duplicate papers in the Office.

Official papers filed by fax should be directed to **571-273-8300**. Faxed draft or informal communications with the examiner should be directed to ***571-273-0893.***

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

/Lorraine Spector/ , Ph.D.
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Art Unit 1647